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Differential effects of cyclosporine and tacrolimus on arterial function

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Summary

Cardiovascular complications are the leading cause of death in renal transplant recipients and constitute one of the leading causes of graft failure. Calcineurin inhibitors (CNI) induce an acceleration of atherosclerotic processes in the arterial wall. There are conflicting data whether cyclosporine A (CsA) and tacrolimus (Tac) differ in their deleterious effects on arterial stiffening. The present study combines several measurement techniques to provide a global and reliable assessment of the differential effects of CNI on the gold-standard parameters of arterial function. Pulse wave analysis was performed by the SphygmoCor (AtCor®), HEM-9000AI (Omron®), and CR-2000 device (Hypertension Diagnostics®) in 56 stable renal transplant recipients (29 CsA, 27 Tac). Groups were homogeneous for age, gender, body mass index, time on dialysis prior to transplantation, and graft function. Whereas systolic and diastolic blood pressure, central aortic blood pressure, cardiac index, large and small artery compliance index (C_1 and C_2), and pulse wave velocity did not significantly differ between CsA and Tac, augmentation index (AI_{75}) was significantly lower in patients treated with Tac. This finding was consistent as assessed by two different measurement systems ($P < 0.05$). Compared to CsA, Tac has a favorable impact on augmentation index, a strong independent predictor for cardiovascular mortality.

Introduction

Cardiovascular events are the leading cause of death in renal transplant recipients and constitute one of the leading reasons of graft failure [1,2]. Within 36 months of transplantation, almost 40% of kidney recipients suffer from a cardiovascular event [3]. Furthermore, progressive arteriosclerotic wall changes play a crucial role in the development of chronic allograft injury and therefore deteriorate renal allograft function. Hence, minimization of traditional and nontraditional cardiovascular risk factors is a cornerstone in the maintenance therapy of renal transplant recipients. Attempts have been made to measure the extent of vascular calcification in a standardized noninvasive manner. Computerized pulse wave analysis has provided several parameters that mirror arterial stiffness including pulse wave velocity (PWV), augmentation index (AI), and large/small artery compliance (C_1/C_2). Since the progression of arteriosclerosis is massively accelerated in uremia, it is not surprising that successful renal transplantation has been shown to reduce these markers of arterial stiffness [4–7]. Ignace *et al.* found that the decrease of PWV after renal transplantation is age dependent and predominantly occurs in elderly patients [7]. Despite an improvement of arterial function after renal transplantation, it has to be stated that stiffness remains largely increased compared with the healthy population [8]. Furthermore, the decrease of arterial stiffness may have a transient character [6].

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On the one hand, the persistent elevation of arterial stiffness after renal transplantation may be explained by irreversible arteriosclerotic wall changes that evolved prior to transplantation. On the other hand the immunosuppressive regimen may counteract the beneficial vascular effects of the transplantation. Calcineurin inhibitors (CNI) still constitute the basis of most maintenance immunosuppressive regimens after kidney transplantation. CNI are potent vasoconstrictors (acute CNI toxicity) and promoters of intravascular fibrosis leading to obliterative arteriolopathy (chronic CNI toxicity). Several authors have described a deleterious effect of cyclosporine A (CsA) on arterial function measured by AI and PWV [4,5,9,10]. Consistently, PWV decreases after conversion from cyclosporine (CsA) to an mTOR-inhibitor [11]. There is controversial data on the question, whether the vascular effects of tacrolimus (Tac) may be less harmful than those of CsA. Whereas Strozecki *et al.* reported a lower PWV in Tac regimens compared with cyclosporine, Martinez-Castelao found no difference in the elasticity of small arteries [9,12]. Elasticity of large arteries, however, was significantly lower in CsA than in Tac patients [12]. Ferro *et al.* described a significantly lower AI in Tac than in CsA but no difference in the transit time of the reflected wave as an indicator or arterial stiffness [10]. To complete the confusion, acute ingestion of CsA (Neoral®; Novartis, Basel, Switzerland) may even decrease AI, speculatively ascribable to the Vitamin E containing diluents vehicle [13].

These conflicting results may partially be caused by the use of different measurement systems. To date, there is no study that makes use of different techniques for the measurement of arterial stiffness. The present work investigates the differential effects of CNI on the gold-standard parameters of arterial function combining different techniques of pulse wave analysis.

Patients and methods

Study population and protocol

Patients were recruited from the outpatient clinic and ward of our transplant center. For reasons of comparability of pulse wave analysis, bilateral fistula was regarded as an exclusion criterion. Inclusion criteria were written informed consent for participation, successful (requiring no dialysis therapy at the time of inclusion in the study) renal transplantation >16 weeks ago, and a CNI containing immunosuppressive regimen. Transplantation <16 weeks ago was defined as an exclusion criterion, since we have previously shown that changes in pulse wave properties may have a variable character in the first 3 months after transplantation [6]. The standard immunosuppressive regimen in our transplant program consists of CsA, mycophenolic acid, and prednisolone. Conversion to Tac is performed in case of rejection or side effects of CsA. In the present study population it took place after a mean of 25.5 ± 50.6 months. Fourteen (51.9%) patients in the Tac group were converted ascribable to rejection, 13 (48.1%) referable to side effects of CsA. Informed consent for participation in the study was obtained from all patients prior to inclusion in the study. Approval for the study was obtained from the local ethical committee.

Fifty-six patients were enrolled in the study (53 cadaveric grafts, three live donor transplantations). Immunosuppression included CsA in 29 cases and Tac in 27 cases. Epidemiologic information, data on transplantation and graft function, cause of end stage renal disease, and concomitant diseases are presented in Table 1. Data on immunosuppression and cardiovascular medication are presented in Table 2. Patients in the CsA and Tac group had been on dialysis for a median of 40 and 71 months, respectively, and had a functioning graft since a median of 74 and 51 months. Mean age was 53.2 ± 12.9 years. The predominant cause of end stage renal failure was glomerulonephritis followed by polycystic kidney disease. The majority of the probands had a triple immunosuppressive regimen; the most frequent combination was CNI, mycophenolic acid, and prednisolone. The mean number of antihypertensive drugs was 3, the most frequent drug was a diuretic, all but one patient were treated for hypertension. In both groups, the proportion of diabetic patients was low (CsA: three patients, 10.3%; Tac: five patients, 18.5%). There was only one case of diabetic nephropathy leading to end stage renal failure (CsA group).

Assessment of augmentation index by the Omron HEM-9000AI device

Hemodynamic measurements were conducted in a quiet clinical research laboratory at a constant ambient temperature of 20–22 °C between 12 and 14 AM, at least 3 h and on average 4–6 h after ingestion of CNI as published previously [14]. Since CNI levels might acutely influence arterial elasticity, all the measurements were performed at this defined span of time to assure comparability of results. All measurements were performed by the same person. Patients were resting in a supine position for 15 min before the measurement procedure was started. AI, systolic blood pressure, diastolic blood pressure, and heart rate were measured by the HEM-9000AI device (Omron Healthcare®, Kyoto, Japan). Blood pressure was measured oscillometrically at the nonfistula arm. AI was assessed by computerized radial artery pulse wave analysis. The HEM-9000AI device makes use of a multi-sensor array technology to detect pulse waves by applanation tonometry. The AI was calculated as 'AI(%) = (Peak of reflected pulsewave/peak of the ejected wave) × 100' (Fig. 1). Since AI

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Table 1. Comparison of epidemiologic, vascular, and renal data, cause of end stage renal failure, and concomitant diseases of patients with cyclosporine and tacrolimus.

Parameter	Cyclosporine	Tacrolimus	*P*
Epidemiologic data			
Number of subjects included	29	27	
Male (%)	15 (51.7)	18 (66.7)	0.29
Female (%)	14 (48.3)	9 (33.3)	
Age (years)	54.6 ± 12.0	51.7 ± 13.8	0.41
Body mass index (kg/m^2)	25.5 ± 4.6	25.4 ± 4.8	0.98
Vascular parameters			
Brachial systolic blood pressure (mmHg)	134.5 ± 17.3	133.9 ± 18.9	0.90
Brachial diastolic blood pressure (mmHg)	70.9 ± 13.6	73.6 ± 15.3	0.50
Brachial pulse pressure (mmHg)	63.6 ± 14.3	60.3 ± 12.3	0.37
Cardiac index (ml/min/m^2)	2.8 ± 0.3	2.8 ± 0.3	0.48
Heart rate (1/min)	71.5 ± 7.7	69.9 ± 10.7	0.54
AI (Omron)	80.7 ± 12.6	73.6 ± 16.1	0.07
AI_{75} (Omron)	79.5 ± 12.4	71.9 ± 13.9	0.04
AI_{75} (SphygmoCor)	24.7 ± 9.3	19.1 ± 9.7	0.04
PWV (m/s)	8.9 ± 2.2	8.5 ± 1.7	0.50
Aortic systolic blood pressure (mmHg, SphygmoCor)	118.5 ± 21.6	117.5 ± 16.0	0.86
Large artery elasticity index (C_1, ml/mmHg × 10)	10.4 ± 3.0	11.3 ± 3.6	0.35
Small artery elasticity index (C_2, ml/mmHg × 100)	4.8 (2.8–6.5)	5.3 (3.8–7.6)	0.14
Renal data			
Live donor transplantation (%)	2 (6.9)	1 (3.7)	1.0
Time on dialysis (months)	40.0 (17.0–84.3)	71.5 (32.3–87.3)	0.31
Vascular access (fistula)			
Proximal (%)	1 (3.4)	3 (11.1)	
Distal (%)	9 (31.0)	9 (33.3)	
No functioning fistula (%)	19 (65.5)	15 (55.6)	
Time since transplantation (months)	74.0 (26.8–148.5)	51.5 (12.3–108.0)	0.22
eGFR (ml/min, calculated by CKD-Epi formula)	39.3 ± 18.9	38.1 ± 23.9	0.66
Albuminuria (mg/l)	203.8 ± 336.7	121.4 ± 137.6	0.78
Donor age (years)	43.1 ± 17.9	52.2 ± 13.0	0.04
Cold ischemia time (h)	14.7 ± 6.9	13.9 ± 5.2	0.65
Cause of end stage renal failure (%)			
Glomerulonephritis	5 (17.2)	9 (33.3)	
Polycystic kidney disease	6 (20.7)	5 (18.5)	
Benign nephrosclerosis	3 (10.3)	1 (3.7)	
Diabetic nephropathy	1 (3.4)	0 (0)	
Interstitial nephritis	2 (6.9)	5 (18.5)	
Alport syndrome	2 (6.9)	1 (3.7)	
Hereditary dysplasia/reflux	2 (6.9)	0 (0)	
Amyloidosis	1 (3.4)	0 (0)	
Systemic sclerosis	1 (3.4)	0 (0)	
Unknown	6 (20.7)	6 (22.2)	
Concomitant diseases			
Hypertension (%)	28 (96.6)	27 (100)	1.0
Diabetes mellitus (%)	3 (10.3)	5 (18.5)	0.46
Coronary heart disease (%)	4 (13.8)	7 (26.0)	0.32
Hyperlipidemia (%)	12 (41.4)	13 (48.1)	0.79
Cholesterol (mg/dl)	209.8 ± 61.0	213.0 ± 53.1	0.85
LDL-cholesterol	116.8 ± 46.6	122.2 ± 38.9	0.67
HDL-cholesterol	45.6 ± 17.5	47.5 ± 13.0	0.68
Triglycerides	231.4 ± 141.0	200.9 ± 116.0	0.49
Tobacco abuse (%)	6 (20.7)	7 (26.0)	0.76

Numeric data are presented as mean ± standard deviation and were tested for statistically significant differences by unpaired two-tailed *t*-tests in case of normal distribution. Otherwise, they are presented as median and interquartile range and comparison is performed by the Mann–Whitney *U*-test (C_2, time on dialysis, time since transplantation). Categorical parameters (gender, live/cadaveric donation, presence of a disease) were compared by Fisher's exact test.

$P < 0.05$ was regarded statistically significant.

AI, augmentation index; eGFR, estimated glomerular filtration rate; PWV, pulse wave velocity; CKD-Epi, chronic kidney disease epidemiology collaboration.

depends on heart rate, the device adjusts AI to a heart rate of 75/min (AI_{75}). The device has been successfully used in transplant recipients before [14]. Three measurements were performed and mean values for blood pressure and AI were used for statistical evaluation.

Assessment of large and small artery elasticity index

Measurements were performed as published previously [6]. Systolic blood pressure, diastolic blood pressure, and heart rate were measured oscillometrically. Arterial elasticity was assessed using computerized radial artery pulse wave analysis by means of the CR-2000 instrument (Hypertension Diagnostics®, Eagan, MN, USA). Radial artery waveforms were recorded for 30 s at the non-fistula arm of each subject with an arterial tonometer sensor. Data were digitized at 200 samples/s. The beginnings of systole, peak systole, onset of diastole, and end diastole for all pulse waves in this 30 s period were determined. After averaging the pulse waves of the analysis period an algorithm developed by Cohn *et al.* (Hypertension Diagnostics®) was applied to define a third-order equation approximating the waveform and diastolic decay [15]. According to a modified Windkessel model, pulse contour analysis of the diastolic pressure decay allows an estimation of 'oscillatory' small artery and 'capacitive'

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Table 2. Medication of the study population.

	Cyclosporine (n = 29)	Tacrolimus (n = 27)	P
Immunosuppression (%)			
Triple immunosuppression	21 (72.4)	21 (77.8)	0.76
Mono/dual immunosuppression	8 (27.6)	6 (22.2)	0.76
Cyclosporine	29 (100)	0 (0)	<0.01
Tacrolimus	0 (0)	27 (100)	<0.01
mTOR inhibitors	0 (0)	0 (0)	n.a.
Mycophenolic acid	23 (79.3)	20 (74.1)	0.76
Azathioprine	2 (6.9)	2 (7.4)	1.0
Prednisolone	25 (86.2)	25 (92.6)	0.67
Antihypertensives			
Number of antihypertensives (median, range)	3 (1–5)	3 (0–5)	0.11
Calcium channel blockers (%)	16 (55.2)	16 (59.3)	0.79
ACE-Inhibitors/ARB (%)	10 (34.5)	7 (25.9)	0.59
Beta blockers (%)	26 (89.7)	24 (88.9)	1.0
Diuretics (%)	25 (86.2)	19 (70.4)	0.20
Others			
Statins (%)	11 (37.9)	9 (33.3)	0.79

ACE-inhibitors, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

large artery elasticity (C_1 and C_2). The model uses an estimated cardiac output, which is a multivariate function of ejection time, heart rate, body surface area, and age can be determined from the arterial pressure waveform, as validated by previous invasive and noninvasive studies [15]. In the Results section, we present cardiac index, which is cardiac output divided by body surface. The method has been used in studies on hemodialysis [16] and transplant patients before [6,12,17]. Three measurements were performed and the mean value was used for statistical evaluation.

Assessment of pulse wave velocity, aortic blood pressure, and augmentation index by the SphygmoCor device

Measurements were performed in the same session as the measurements described above. Blood pressure was measured oscillometrically using the Omron HEM-9000AI device as described above. Applanation tonometry was performed using a SphygmoCor device (AtCor Medical®, Sydney, NSW, Australia) as recommended [18]. In brief, recording of radial pressure waveforms was performed by a high-fidelity micromanometer placed on the tip of a hand-held tonometer (Millar Instruments®, Houston, TX, USA), which was applied to the surface of the skin overlying the radial artery at the non-fistula arm. Pulse waves were recorded for 12 s. In accordance with the manufacturer's recommendations several recordings were taken if needed to accomplish recommended quality control criteria, namely a quality index ≥ 80%. Transformation of peripheral pressure waveforms was performed by means of a generalized transfer function [19], which had been previously validated by using intra-arterially measured pressure waves [20]. Calibration of the recorded pressure waveforms was done by using the brachial systolic and diastolic blood pressure values. AI was calculated as 'AI(%) = (Augmentation pressure/pulse pressure) × 100' (Fig. 1). Augmentation pressure represents the augmentation (mmHg) in central systolic pressure referable to the return of the reflected wave at the aorta (Fig. 1). PWV was calculated from measurements of pulse transit time and the distance traveled between two recording sites as 'PWV = distance/transit time'. An electrocardiogram (ECG) was used to determine the start of the pulse-wave. The mean of 12 s of tonometer recorded pulse-waves at the femoral and carotid artery were used to determine the arrival of the pulse-wave at the peripheral recording site (aortic PWV). The distance was

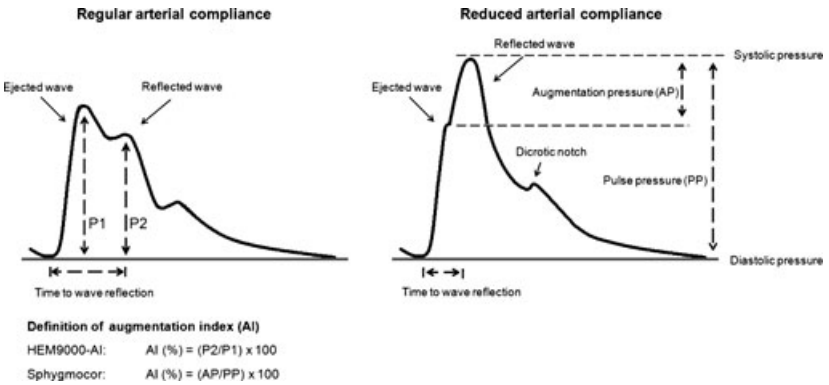

Figure 1 Arterial pulse wave in a subject with normal arterial compliance and a subject with reduced arterial compliance. Arterial stiffening results in a shortened transit time of the arterial wave leading to an augmentation of the ejected wave by the reflected wave. The figure illustrates the two different definitions of augmentation index [Omron®: AI = Pressure of rejected wave (P2)/pressure of ejected wave (P1); AtCor®: AI = Augmentation pressure (AP)/pulse pressure (PP)].

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measured between the recording sites and the suprasternal notch. In analogy to the Omron device, there is a software-based correction of AI to a heart rate of 75/min (AI_{75}). The mean value of two consecutive measurements was used for statistical analysis.

Statistical analysis

Distribution of numeric data was analyzed by the Kolmogorov–Smirnov test and histograms. In case of normal distribution, data are presented as mean ± standard deviation, otherwise as median and interquartile range. In case of normal distribution, comparison of the numeric parameters was performed by two-sided two-sample *t*-tests, otherwise by the Mann–Whitney *U*-test. Comparison of categorical parameters was performed by Fisher's exact test in case of dichotomy and by Pearson χ^2 test in case of polychotomy. $P < 0.05$ was regarded statistically significant. All statistical analyses were done using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Fifty-six patients were enrolled in the study. Twenty nine of these patients were administered CsA, 27 were administered Tac. Pulse wave analysis by means of the Omron® device was successful in all patients with CsA and in all but one patient with Tac. Pulse wave analysis by the AtCor® device provided results in 28 patients with CsA and 24 patients with Tac. Assessment of small and large artery compliance by the CR-2000 instrument was successful in all the patients.

Epidemiologic, renal, and vascular data of the two groups are presented in Table 1. The CsA and Tac group showed no significant differences with regard to gender distribution, age, and body mass index. There were two live donor transplantations in the CsA group and one in the Tac group. Time of dialysis prior to transplantation, time since transplantation, estimated glomerular filtration rate (eGFR) {calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula [21]}, and cold ischemia time did not show any significant differences in the two groups as well ($P > 0.05$ each). Donor age, however, was significantly lower in the CsA group (43.1 ± 17.9 vs. 52.2 ± 13.0 years, *P* 0.04). Presence of concomitant diseases including diabetes, hypertension, hyperlipidemia, and lipid profile were not significantly different in the two groups ($P > 0.05$ each).

Systolic and diastolic brachial blood pressure values were comparable in the two groups (*P* 0.90 and 0.50, respectively). Hence, brachial pulse pressure was not significantly different in the CsA and Tac group as well (*P* 0.37). There was no differential impact of the two CNIs on heart rate (*P* 0.54, Table 1). Measurements with the Omron device revealed a trend to a lower AI in the Tac group (*P* 0.07). After adjustment to a pulse rate of 75/min (AI_{75}), the difference was significant (*P* 0.04). These findings were confirmed by the measurements with the AtCor® device: AI_{75} was significantly higher in the CsA group (*P* 0.04). PWV revealed no significant difference in the two groups (*P* 0.50). SphygmoCor® pulse wave analysis furthermore allowed an assessment of systolic aortic blood pressure. Mean systolic aortic blood pressure was comparable in the two groups (0.86). Mean large and small artery elasticity indices (C_1 and C_2) were slightly higher in the Tac group without reaching significance (*P* 0.35 and 0.32, respectively). Mean cardiac index was almost identical in the two groups (*P* 0.48).

Discussion

In recent years several studies on the impact of CNIs on arterial function after renal transplantation have been published with conflicting results. A potential reason for the diverging results may be that the authors made use of different measurement techniques. The present work combines various techniques of pulse wave analysis for the first time. Apart from the assessment of large and small artery elasticity indices, it provides the gold standard of PWV measurement and two different techniques of AI assessment. Thus, it is intended to provide a detailed picture of the differential effects of the two CNIs on current parameters of arterial function.

The central finding of the study is a significantly lower AI_{75} in presence of Tac as compared with CsA. This finding was established by both the AtCor® and the Omron® system making a 'false positive' result rather improbable. Our findings are in accordance with the results of Ferro *et al.*, who assessed the contribution of several classical and nonclassical cardiovascular risk factors on aortic pressure augmentation in renal transplant recipients. The presence of CsA in the immunosuppressive regimen significantly contributed to an increase in AI in multivariate analysis [10]. The AtCor® system was used in this study. With regard to Ferro's and our findings, the transient decrease of AI that has been described after the acute ingestion of CsA (Neoral®) may be interpreted rather as a potential effect of the Vitamin E containing diluents vehicle than of CsA itself [13]. London *et al.* have shown that the AI is an independent predictor of cardiovascular risk in hemodialysis patients [22]. An increased aortic augmentation pressure causes increased pressure during systole and thus enhances left ventricular workload, which promotes left ventricular hypertrophy [23], a strong independent predictor for all-cause mortality [24]. Since AI is

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lower in presence of Tac than of CsA it may be speculated that Tac might have a less deleterious impact on cardiovascular outcome than CsA. A crucial question is, whether or not there are other aspects that could explain the difference of AI in the two groups. The prevalence of classical proarteriosclerotic factors including diabetes, hyperlipidemia, hypertension, and tobacco use, however, is not significantly different in the two groups. Drugs like statins and antihypertensives, which are known to have an impact of endothelial function and AI, are comparable in the two groups as well. Finally, the presence of an arteriovenous fistula has effects on the arterial pulse wave profile [25,26]. Therefore, we defined bilateral fistula as an exclusion criterion. Moreover, the CyA and the Tac group were homogeneous for location of vascular access as presented in Table 1.

Data on the differential effects of the two CNIs on PWV are sparse and inhomogeneous in the literature. In accordance with Ferro *et al.* we did not reveal a significant difference between CsA and Tac. Carotid-femoral PWV is a direct measure of regional aortic stiffness. AI, however, is a relative measure of wave reflections that contribute to central pulse pressure. It depends on many factors including PWV, traveling distance of pressure waves (body height), heart rate, and the reflective properties of the arterial system including small artery compliance and endothelial function [27]. Hence, it is not inconsistent that there is a significant difference in AI but no difference in PWV. Moreover, there may be a selection bias that potentially could impede a lower PWV in the Tac group: The majority of subjects in the Tac group had been converted from CsA to Tac ascribable to cellular or humoral rejection. Both cellular and antibody-mediated rejections of a renal allograft are initiated at the vascular endothelium. Therefore, rejection may lead to endothelial dysfunction finally resulting in a reduction of arterial compliance. Mean compliance of large and small arteries tended to be higher in the Tac group without reaching significance. It remains open whether a larger size of study population or a lack of the selection bias mentioned above would have been able to produce a significant difference in elasticity indices and PWV. Finally, it has to be kept in mind that our findings describe aortic PWV measured between carotid and femoral artery. We do not know whether CNI affect aorta and other arteries, e.g. muscular conduit arteries, in the same way. Changes in stiffness of these arteries may affect AI (radial tonometry) but not aortic PWV.

How can it be explained that the AI_{75} is higher in presence of CsA than in presence of Tac? The lack of a significant difference in PWV suggests that the lower AI_{75} in Tac patients is not a consequence of a lower aortic stiffness. Since body height was not significantly different in both groups and AI was adjusted for heart rate, the reflective properties determined by small artery vascular tone have to be different. CNIs exert a broad variety of effects on the vasculature. Both CsA and Tac are potent vasoconstrictors. Although the exact mechanism is unknown, there is a substantial impairment of endothelial cell function, leading to reduced production of vasodilators (prostaglandins and nitric oxide) and enhanced release of vasoconstrictors (endothelin and thromboxane) [28–30]. CsA causes an increase of free reactive oxygen species [31]. Furthermore, it may increase sympathetic tone [32]. In renal transplant patients these mechanisms are of relevance, since they mediate acute CNI nephrotoxicity by vasoconstriction of afferent and efferent glomerular arterioles. Although CsA and Tac are known to have very similar intrinsic properties, the vasoconstrictive effects of CsA are reported to be more pronounced than those of Tac [33]. An increased vasoconstriction of the small arteries induces an increase in the difference of vascular impedance yielding a more intense reflection of the pulse wave. Furthermore, AI depends on endothelial function. CsA is known to impair endothelium-dependent NO production and vasodilation in renal transplant recipients [34]. Recently, it has been demonstrated that Tac does not alter endothelium-dependent vasodilation (flow-mediated dilation, FMD) after orthotopic liver transplantation [35]. Thus, a less deleterious effect of Tac on endothelial function might be another explanation for the differential impact of Tac and CsA on AI_{75}.

The extent of atherosclerotic wall changes in a transplant recipient crucially depends on the time of dialysis dependency prior to transplantation. In uremia there is a deficiency of inhibitors of vascular calcification and vascular smooth muscle cells transform to osteoblast-like cells leading to rapidly progressive arteriosclerosis. After transplantation the level of uremic toxins decreases and the stimulus for vascular calcification is reduced. The time since transplantation was not significantly different between Tac and CsA patients but tended to be longer in the CsA group. Therefore, the time of exposure of CNI tended to be longer in the CsA group. On the other hand, there are three aspects suggesting a reduced risk for arterial stiffening in the CsA group: As discussed above, there is a selection bias in favor of CsA since the majority of patients in the Tac group had a history of rejection. Secondly, donor age was significantly higher in the Tac group. It has been shown that older age of kidney donor is independently associated with an increase of arterial stiffness of the recipient [36]. Thus, both rejections and higher donor age predispose to an increased arterial stiffness. Finally, the time on dialysis tended to be longer in the Tac group. Nevertheless, the Tac patients showed a lower AI_{75} than the CsA patients.

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Systolic blood pressure, diastolic blood pressure, and pulse pressure were not significantly different in the two groups although CsA is known to increase blood pressure more intensely than Tac. Post-transplant management of the transplant recipients, however, demanded the same blood pressure targets of antihypertensive therapy in both groups. Interestingly, the median number of antihypertensive drugs was identical in both groups in the present study population. The final question to be answered is: Why should we pay attention to a surrogate parameter like the AI, if we are actually interested in cardiovascular mortality? The answer is simple: Since currently it is the best we can get. Large-scale studies like ELITE-Symphony [37] have required huge efforts to have the statistical power for revealing differential effects of immunosuppressive drugs on graft outcome 1 year post-transplant. A prospective trial on the impact of immunosuppressants on cardiovascular events or even cardiovascular mortality, however, would require a much larger study population and an observation period of many years. With regard to the necessary financial resources, a study like this – although most desirable – will probably remain an illusion in the near future. In this context, a well validated vascular parameter like the AI, that provides a footprint of atherosclerotic wall changes and constitutes a reliable prognostic marker of cardiovascular risk, may be the most promising alternative.

In summary, the present study provides evidence for a favorable impact of Tac on arterial function as compared to CsA. Different techniques of measurement confirmed a lower AI_{75}, an independent predictor for cardiovascular mortality.

Authorship

FS: participated in research. CB: participated in research. SS: participated in data analysis. MvdG: participated in data analysis. WZ: participated in research design and review of manuscript. THW: idea, research design, data analysis, writing of the manuscript.

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